

WHAT IS CLAIMED IS:

1. A method of examining a reactivity of a first sample with a plurality of second samples having different properties from one another, comprising the steps of:

preparing a substrate with said first sample bound thereto in a defined region;

arranging said plurality of second samples within said region independently of one another; and

testing the reactivity of said first sample with each of said second samples.

2. The examination method according to claim 1, wherein said reactivity is a bonding capability between said first sample and said second samples.

3. The examination method according to claim 2, wherein said bonding capability is based on complementation of nucleic acid strands.

4. The examination method according to claim 1, wherein said first sample is originated from an organism, and said second samples have known properties.

5. The examination method according to claim 4, wherein said second samples are synthesized.

6. The examination method according to claim 5,  
wherein said first sample includes a nucleic acid  
originated from an organism and having an unknown base  
sequence, and said second samples include synthesized  
5 nucleic acids having known base sequences.

7. The examination method according to claim 6,  
wherein said first sample includes a set of mRNAs  
extracted from an organism.

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8. The examination method according to claim 6,  
wherein said first sample includes a cDNA library  
synthesized based on mRNAs extracted from an organism.

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9. The examination method according to claim 4,  
wherein said first sample includes a nucleic acid  
originated from an organism and having an unknown base  
sequence, and said second samples include synthesized  
chemicals.

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10. The examination method according to claim 4,  
wherein said first sample includes a nucleic acid  
originated from an organism and having an unknown base  
sequence, and said second samples include purified  
25 proteins.

11. The examination method according to claim 1,

wherein said first sample has a known property, and  
said second samples are originated from an organism.

12. The examination method according to claim 11,  
5 wherein said first sample includes a gene having a  
known sequence.

13. The examination method according to claim 11,  
wherein said first sample includes a cloned oncogene  
10 fragment, and said second samples include nucleic acids  
originated from an organism.

14. The examination method according to claim 1,  
wherein said first sample includes a protein fragment  
15 extracted from an organism, and said second samples  
include purified proteins of a single type.

15. The examination method according to claim 1,  
wherein said first sample includes a purified protein  
20 of a single type, and said second samples include  
protein fragments extracted from an organism.

16. The examination method according to claim 4,  
wherein said first sample includes a protein fragment  
25 originated from an organism, and said second samples  
include synthesized chemicals.

17. The examination method according to claim 4, wherein said first sample includes a purified protein of a single type, and said second samples include synthesized chemicals.

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18. The examination method according to claim 1, wherein said first sample includes a synthesized chemical, and said second samples include nucleic acids extracted from an organism.

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19. The examination method according to claim 1, wherein said first sample includes a synthesized chemical, and said second samples include protein fragments extracted from an organism.

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20. The examination method according to claim 1, wherein said first sample is comprised of a plurality of samples having different properties, and each of said plurality of samples is bound to one of partitioned regions forming a matrix on the substrate.

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21. The examination method according to claim 20, wherein said first sample includes nucleic acids originated from different biological species, tissues or cells.

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22. The examination method according to claim 20,

wherein said first sample includes proteins extracted from different biological species, tissues or cells.

23. The examination method according to claim 20,  
5 wherein the density of said matrix is  $400/\text{cm}^2$  or lower.

24. The examination method according to claim 20,  
wherein an array of spots of said second samples is  
arranged in each of said partitioned regions in a  
10 common arrangement.

25. The examination method according to claim 1,  
wherein said substrate is made of glass.

26. The examination method according to claim 1,  
15 wherein said first sample is fixed on the substrate by  
electrostatic bonds.

27. The examination method according to claim 1,  
20 wherein said first sample is fixed on the substrate by  
covalent bonds.

28. The examination method according to claim 27,  
wherein said first sample is bound to said substrate  
25 through a chemical reaction of maleimide groups  
introduced to a glass surface of the substrate with  
thiol groups possessed by said first sample.

29. The examination method according to claim 28, wherein said first sample includes a protein, and said thiol groups are cycteine groups of the protein.

5           30. The examination method according to claim 28, wherein said maleimide groups are introduced by introducing amino groups to the glass surface and then reacting said amino groups with N-(6-maleimidocaproyloxy)succinimide.

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31. The examination method according to claim 28, wherein said maleimide groups are introduced by introducing amino groups to the glass surface and then reacting said amino groups with succinimidyl 4-(maleimidophenyl)butyrate.

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32. The examination method according to claim 28, wherein said chemical reaction is a reaction between an epoxy group introduced to the glass surface of the substrate and an amino group possessed by said first sample.

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33. The examination method according to claim 30, wherein said amino group is an amino group existing in a nucleic acid base.

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34. The examination method according to claim 1,

wherein said substrate has a surface previously partitioned by a wall member to define sections forming a matrix, and biological samples having different properties are previously bound to the respective sections as the first sample.

35. The examination method according to claim 34, wherein each of said sections has a hydrophobic wall portion and a hydrophilic bottom portion.

36. The examination method according to claim 35, wherein said wall member has a thickness in the range of 1 to 20  $\mu\text{m}$ .

37. The examination method according to claim 1, wherein said second samples are arranged as spots with a diameter of 200  $\mu\text{m}$  or smaller.

38. The examination method according to claim 1, wherein said second samples are arranged as spots with a density of 400/cm<sup>2</sup> or higher.

39. The examination method according to claim 1, wherein said second samples are supplied by an ink-jet method.

40. The examination method according to claim 39,

wherein said second samples supplied by the ink-jet method include nucleic acids having a base pair length in the range of 2 to 5000 pairs.

5           41. The examination method according to claim 40, wherein said nucleic acids supplied by the ink-jet method are supplied as an aqueous solution having a concentration in the range of 0.05 to 500  $\mu$ M.

10           42. The examination method according to claim 39, wherein said ink-jet method is a bubble jet method.

15           43. The examination method according to claim 1, wherein each of said second samples is supplied by contacting a pin with a solution of the sample and contacting said pin physically with said substrate.

20           44. The examination method according to claim 1, wherein each of said second samples is supplied by sucking a solution of the sample using a capillary and then contacting the tip of said capillary physically with the substrate.

25           45. A biological sample matrix, wherein two or more biological samples of different origins are bound to respective partitioned regions forming a matrix on a substrate.



46. The biological sample matrix according to claim 45, wherein said biological samples include cloned oncogene fragments.

5           47. The biological sample matrix according to claim 45, wherein said biological samples include mRNAs.

10           48. The biological sample matrix according to claim 45, wherein said biological samples include cDNAs.

15           49. The biological sample matrix according to claim 45, wherein said biological samples include a cDNA library.

20           50. The biological sample matrix according to claim 45, wherein said biological samples include two or more types of proteins having different conformations.

25           51. The biological sample matrix according to claim 45, wherein the density of said matrix is  $400/\text{cm}^2$  or lower.

          52. The biological sample matrix according to claim 45, wherein said substrate is made of glass.

53. The biological sample matrix according to claim 45, wherein said biological samples are fixed on the substrate by electrostatic bonds.

5        54. The biological sample matrix according to claim 45, wherein said biological samples are fixed on the substrate by covalent bonds.

10       55. The biological sample matrix according to claim 54, wherein said biological samples are bound to said substrate through a chemical reaction of maleimide groups introduced to a glass surface of the substrate with thiol groups possessed by said biological samples.

15       56. The biological sample matrix according to claim 55, wherein said biological samples include proteins bound to the glass surface through a chemical reaction of maleimide groups introduced to the glass surface with thiol groups of cysteine residue of the  
20       protein.

25       57. The biological sample matrix according to claim 55, wherein said maleimide group is introduced by introducing amino groups to the glass surface and then reacting said amino groups with N-(6-maleimidocaproyloxy)succinimide.

58. The biological sample matrix according to claim 55, wherein said maleimide group is introduced by introducing amino groups to the glass surface and then reacting said amino groups with succinimidyl 4-  
5 (maleimidophenyl)butyrate.

59. The biological sample matrix according to claim 54, wherein said biological samples include nucleic acids bound to said substrate through a  
10 chemical reaction of epoxy groups introduced to a glass surface of the substrate with amino groups possessed by said nucleic acids.

60. The biological sample matrix according to  
15 claim 45, wherein said two or more biological samples are supplied on the respective partitioned regions on the substrate by an ink-jet method.

61. The biological sample matrix according to  
20 claim 45, wherein said substrate has a surface partitioned by a wall member to define sections forming a matrix, and said two or more biological samples of different origins are bound to the respective sections.

25 62. The biological sample matrix according to claim 61, wherein each of said sections has a hydrophobic wall portion and a hydrophilic bottom

portion.

63. The biological sample matrix according to claim 62, wherein said wall member has a thickness in  
5 the range of 1 to 20  $\mu\text{m}$ .

64. A method of detecting a complex formed between an oligonucleotide of which base sequence is known and a component having a capability of binding to  
10 said oligonucleotide, comprising the steps of:

preparing at least one oligonucleotide of which base sequence is known;

preparing at least two liquid test samples potentially containing a component having a capability  
15 of binding to said oligonucleotide;

binding said oligonucleotide as a probe to a predetermined region on a solid substrate to produce a detection substrate;

arranging a plurality of spots of said test  
20 samples at a predetermined amount to form an array of said test samples within said region with said oligonucleotide bound thereto;

detecting whether a complex between said oligonucleotide and said component is present or not  
25 for each of said plurality of spots; and

determining whether or not said component is contained in each of said liquid test samples, or how

strong its binding capability to said oligonucleotide is, based on said detection.

5        65. The detection method according to claim 64, wherein said oligonucleotide bound to said detection substrate has a base sequence with a base length of 2 to 100.

10        66. The detection method according to claim 64, wherein said liquid test samples are solutions each containing at least one nucleic acid of which base sequence is unknown, detection is made whether a complex between said oligonucleotide and said nucleic acid is formed or not for each of said test samples to  
15        thereby determine whether or not said nucleic acid contains a base sequence complementary to the known base sequence of said oligonucleotide functioning as said component having a capability of binding to said oligonucleotide.

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      67. The detection method according to claim 66, wherein said nucleic acid contained in each of said liquid test samples includes a set of mRNAs extracted from an organic tissue.

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      68. The detection method according to claim 66, wherein said nucleic acid contained in each of said

liquid test samples includes a cDNA library prepared based on a set of mRNAs extracted from an organic tissue.

5           69. The detection method according to claim 66, wherein said nucleic acid contained in each of said liquid test samples has a base length of 2 to 5000.

10           70. The detection method according to claim 64, wherein said liquid test samples are solutions each containing at least one protein, the proteins contained in said test samples being different from one another.

15           71. The detection method according to claim 64, wherein said liquid test samples are solutions each containing at least one chemical, the chemicals contained in said test samples being different from one another.

20           72. The detection method according to claim 64, wherein said liquid test samples are extracts from different biological species, tissues or cells.

25           73. The detection method according to claim 64, wherein a plurality of oligonucleotides having known base sequences different from one another are used as a probe, and said detection substrate has a plurality of

predetermined sections arranged in a matrix form to which said oligonucleotides are to be bound, respectively.

5           74. The detection method according to claim 73, wherein said plurality of oligonucleotides are bound to said sections to constitute a matrix at a density of 400/cm<sup>2</sup> or lower, said sections having the same area as one another.

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75. The detection method according to claim 73, wherein said test samples are spotted in an array form in each of said sections to which said plurality of oligonucleotides having known base sequences different from one another are bound so that the spot positions in each section are arranged in the same way as one another.

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76. The detection method according to claim 64, wherein said solid substrate used as said detection substrate is made of glass.

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77. The detection method according to claim 64, wherein said oligonucleotide is fixed on the detection substrate by covalent bonds.

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78. The detection method according to claim 77,

wherein said oligonucleotide is fixed on the detection substrate by covalent bonds formed through a chemical reaction of maleimide groups introduced to a glass surface of the substrate used as said solid substrate  
5 with thiol (-SH) groups possessed by said oligonucleotide.

79. The detection method according to claim 78,  
wherein said maleimide groups introduced to the glass  
10 surface is formed by first introducing amino groups to the glass surface and then reacting N-(6-maleimidocaproyloxy)succinimide with the amino groups.

80. The detection method according to claim 78,  
15 wherein said maleimide groups introduced to the glass surface is formed by first introducing amino groups to the glass surface and then reacting succinimidyl 4-(maleimidophenyl)butyrate with the amino groups.

81. The detection method according to claim 77,  
20 wherein said oligonucleotide is fixed on the detection substrate by covalent bonds through a chemical reaction of epoxy groups introduced to a glass surface of the substrate used as said solid substrate with amino  
25 groups possessed by said oligonucleotide.

82. The detection method according to claim 64,



wherein said detection substrate has a surface  
previously partitioned to form a plurality of sections,  
and two or more different types of oligonucleotides of  
which base sequences are known are previously bound to  
5 the sections, respectively, in a matrix form.

83. The detection method according to claim 82,  
wherein said sections previously formed on the surface  
of said detection substrate are separated from each  
10 other by a wall member and each section having a  
hydrophobic wall portion and a hydrophilic bottom  
portion section is hydrophilic.

84. The detection method according to claim 83,  
15 wherein said wall member has a thickness in the range  
of 1 to 20  $\mu\text{m}$ .

85. The detection method according to claim 64,  
wherein each of the spots of said two or more test  
20 samples formed in each section has a diameter of 200  $\mu\text{m}$   
or lower.

86. The detection method according to claim 64,  
wherein the spots of said two or more test samples  
25 formed in each section is arranged at a density of  
400/cm<sup>2</sup> or smaller.

87. The detection method according to claim 64,  
wherein each of the spots of said two or more test  
samples is formed by supplying a predetermined amount  
of a solution of said test samples by an ink-jet  
5 method.

88. The detection method according to claim 87,  
wherein said two or more test samples are spotted by an  
ink-jet method as a solution containing a nucleic acid  
10 with base length of 100 to 5000, respectively.

89. The detection method according to claim 88,  
wherein said two or more test samples are spotted by an  
ink-jet method as a solution containing a nucleic acid  
15 as a total concentrations of 0.05 to 500  $\mu$ M,  
respectively.

90. The detection method according to claim 88,  
wherein said ink-jet method used for spotting is a  
20 bubble jet method.

91. The detection method according to claim 64,  
wherein the spots of test samples are formed by  
contacting a pin having a tip for collecting sample  
25 solutions with a solution of each test sample to allow  
the sample solution to adhere to the tip of said pin  
for taking a predetermined amount of the solution and

then physically contacting the tip of said pin with a surface of the substrate to transfer said predetermined amount of the solution to the substrate surface.

5           92. The detection method according to claim 64,  
wherein the spots of test samples are formed by sucking  
a solution of each test sample using a capillary having  
a tip for sucking sample solutions thereinto and then  
physically contacting the tip of said capillary with a  
10       surface of the substrate to transfer a predetermined  
amount of the solution to the substrate surface.

          93. A detection substrate with two or more  
oligonucleotides having known base sequences different  
15       from one another fixed on a solid substrate,

          wherein said two or more oligonucleotides are  
bound and fixed on a plurality of predetermined  
sections, respectively, so that one oligonucleotide is  
present in each section, and said plurality of  
20       predetermined sections with oligonucleotides fixed  
therein are arranged in a matrix form on a surface of  
said solid substrate.

          94. The detection substrate according to claim  
25       93, wherein the known base sequence of each of said two  
or more oligonucleotides bound in predetermined  
sections has a base length of 2 to 60.

95. The detection substrate according to claim 93, wherein said plurality of predetermined sections are arranged in a matrix form on the surface of said solid substrate at a density of 400/cm<sup>2</sup> or lower.

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96. The detection substrate according to claim 93, wherein said solid substrate is a glass substrate.

97. The detection substrate according to claim 10 93, wherein said oligonucleotides are fixed on the substrate surface by covalent bonds.

98. The detection substrate according to claim 15 97, wherein said oligonucleotides are fixed on the detection substrate by covalent bonds formed through a chemical reaction of maleimide groups introduced to a glass surface of the solid substrate with thiol groups possessed by said oligonucleotides.

99. The detection substrate according to claim 20 98, wherein said maleimide groups introduced to the glass surface are formed by first introducing amino groups to the glass surface and then reacting succinimidyl 4-(maleimidophenyl)butyrate with the amino 25 groups.

100. The detection substrate according to claim

98, wherein said maleimide groups introduced to the glass surface are formed by first introducing amino groups to the glass surface and then reacting N-(6-maleimidocaproyloxy)succinimide with the amino groups.

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101. The detection substrate according to claim 97, wherein said oligonucleotides are fixed on the detection substrate by covalent bonds through a chemical reaction of epoxy groups introduced to a glass surface of the solid substrate with amino groups possessed by said oligonucleotides.

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102. The detection substrate according to claim 93, wherein said two or more oligonucleotides are fixed in each of said predetermined sections such that one oligonucleotide is present in each section by supplying said two or more oligonucleotides in each of said predetermined sections in a matrix form by printing them by an ink-jet process.

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103. The detection substrate according to claim 93, wherein said two or more oligonucleotides are bound to said plurality of predetermined sections previously partitioned in a matrix form.

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104. The detection substrate according to claim 103, wherein said sections previously formed in a

matrix form on the substrate surface are separated from each other by a wall member and each section has a hydrophobic wall portion and a hydrophilic bottom portion.

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105. The detection substrate according to claim 104, wherein said wall member has a thickness in the range of 1 to 20  $\mu\text{m}$ .

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106. The detection substrate according to claim 104, wherein two or more oligonucleotides are fixed to said previously formed sections in a matrix form by an ink-jet method so that said two or more oligonucleotides are supplied only on the bottom portion of each section.

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107. A method of preparing a detection substrate with two or more oligonucleotides having known base sequences different from one another fixed on a solid substrate, comprising:

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preparing a solid substrate having a surface previously partitioned into a plurality of sections in a matrix form,

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supplying a predetermined amount of two or more oligonucleotides in said predetermined sections so that only one type of said oligonucleotides is present in each section by an ink-jet method, and

fixing the supplied oligonucleotides in the predetermined sections.